

REMARKS

Upon entry of the present amendment, claim 3 will be amended. Claims 2 and 3 will remain pending, with claim 3 being the sole independent claim.

By the amendment herein, claim 3 has been amended to even more explicitly recite the compound or a salt thereof not having substantial reactivity with superoxide and/or NO so that the compound or a salt thereof can specifically measure the peroxy nitrite even in the presence of superoxide and or NO. Support for this amendment appears throughout Applicants' originally filed application in defining over the prior art as used in the rejection of record, as see, for example, page 2, the first paragraph under Disclosure of the Invention; page 5, the paragraph beginning at the bottom of the page; and page 8, the second full paragraph.

Reconsideration of the rejections of record, and allowance of the application in view of the following remarks are respectfully requested.

Discussion of Telephone Interviews

Applicants express appreciation for a telephone interview with Examiner Moss on June 9, 2009 with Applicants' representative Arnold Turk. During this telephone interview, the Examiner was requested to withdraw finality of the May 14, 2009 Office Action as being premature because of the use of US 2002/0182736 A1 to Aldini et al. (hereinafter "Aldini") in the rejections. The Examiner indicated that Aldini was being used to support a position taken in the rejection, and that a request for withdrawal of finality can be presented when filing the written response to the Final Office Action.

Applicants also express appreciation for the courtesies extended by Examiner Kim and Examiner Fritchman to Applicants' representative Arnold Turk during a November 18, 2009 telephone interview in connection with the above-identified application.

During the interview, Applicants' representative reminded the Examiners that the 35 U.S.C.102(b) anticipation rejection had been withdrawn, and the 35 U.S.C.103(a) obviousness rejection and the obviousness-type double patenting rejections had been modified in the Final Office Action to include Aldini.

Arguments were presented that the documents used in the rejections, which include WO 01/64664, which is cited and contrasted in Applicants' specification, do not teach or suggest measuring peroxynitrite, and do not teach or suggest a method of measuring peroxynitrite without being affected by NO or superoxide. Reference was also made to Table 1 on page 8 of Applicants' specification regarding such unexpected specific measurement of peroxynitrite without being affected by superoxide or NO.

The Examiners appeared to contend that the genus of reactive active oxygen species is known in the prior art, and that the species of peroxynitrite would have been obvious. The Examiners specifically referred to Aldini, paragraph [0044], and contended that this paragraph supported the rejection. Applicants' representative argued that peroxynitrite measurement was not obvious so that a *prima facie* case of obviousness had not been established. Moreover, the Examiners were referred to the unexpected showing in Applicants' specification that other reactive oxygen species, which the Examiners contend would have been expected to also be measured, are not measured when Applicants' recited compounds are reacted with peroxynitrite. The Examiners appeared to desire that additional method steps be included in Applicants' claims that further define over the prior art to which arguments were presented that the claims recite reacting the recited compounds and peroxynitrite, and that is not taught or suggested in the prior art.

Applicants' representative also indicated that Applicants would consider amending claim 3 to even more explicitly recite the specific measurement of peroxynitrite. However, the Examiners indicated that the claims already implicitly include such language, and would not change the rejections.

Request for Withdrawal of Finality of the Office Action

The finality of the Office Action dated May 14, 2009 is premature and should be withdrawn. In particular, for the reasons set forth below, the finality of the May 14, 2009 Office Action should be withdrawn because the Office Action has instituted a new ground of rejection that was not necessitated by Applicants' amendment of the claims.

Claim 3 was amended in Applicants' Amendment filed April 9, 2009 by being placed into independent form. The scope of claim 3 was not changed in any manner in the Amendment that would necessitate a new ground of rejection being instituted. However, despite this lack of Applicants' amendment necessitating a new ground of rejection, a new ground of rejection has been made in the May 14, 2009 Office Action. Thus, the finality of the May 14, 2009 Office Action is premature and should be withdrawn.

More specifically, in the Final Office Action, Aldini is used in the rejection to support the position that peroxynitrite is considered a reactive oxygen species and would be a desirable species to measure. In fact, during the above-noted interview, the Examiners supported this assertion of peroxynitrite being a desirable species to measure by relying upon the disclosure of Aldini in paragraph [0044] relating to its disclosure of measuring lipid antioxidant. The Examiners contended that the Aldini rendered the measurement of peroxynitrite as being directed to an analytical procedure.

As set forth in MPEP 706.06(a), Rev. 6, Sept. 2007, pages 700-82 to 700-83 (with emphasis added):

Under present practice, second or any subsequent actions on the merits shall be final, except where the examiner introduces a new ground of rejection that is neither necessitated by applicant's amendment of the claims, nor based on information submitted in an information disclosure statement filed during the period set forth in 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p). Where information is submitted in an information disclosure statement during the period set forth in 37 CFR 1.97(c) with a fee, the examiner may use the information submitted, e.g., a printed publication or evidence of public use, and make the next Office action final whether or not the claims have been amended, provided that no other new ground of rejection which was not necessitated by amendment to the claims is introduced by the examiner. See MPEP § 609.04(b)....

Accordingly, as discussed above, the second action on the merits has prematurely been made final because it includes a new ground of rejection that is neither necessitated by Applicants' amendment of the claims, nor based on information submitted in an Information Disclosure Statement. Applicants should be afforded an opportunity to address the issues raised by Aldini prior to finality of the Office Action. Therefore, withdrawal of the finality of the May 14, 2009 Office Action is respectfully requested.

Art Based Rejection

The following art based rejection is set forth in the Final Office Action.

(a) Claims 2 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/64664 to Nagano (using EP 1 260 580 A1 as English version) as evidenced by US 2002/0182736 A1 to Aldini.

Initially, Applicants once again note that U.S. Patent No. 7,087,766 B2, which is being used in an obviousness-type double patenting rejection is the national stage of Nagano. Accordingly, it is not clear why the rejection is using EP 1 260 580 A1 when U.S. Patent

7,087,766 B2 indicates on its face that it is a national state of WO 01/64664.

Regarding the merits of the rejection, Applicants submit that this ground of rejection is without appropriate basis, and should be withdrawn.

As discussed in Applicants' Amendment Under 37 C.F.R. 1.111, filed April 9, 2009, in Applicants' originally filed specification, beginning at page 1, third full paragraph, peroxynitrite (ONOO⁻) is a typical substance among RNS, and is produced by a reaction of NO and superoxide. Reaction rate of this production reaction is mostly limited by diffusion, and when superoxide produced by NADPH oxidase or the like and NO produced by NO synthetase (NOS) coexist, ONOO⁻ is immediately produced. ONOO⁻ has high oxidation ability, for example, it achieves hydroxylation of an aromatic ring, and has characteristic reactivities such as, for example, efficient nitration of tyrosine.

It is further disclosed that examples of the methods for detecting ONOO⁻ developed so far include (1) a method of performing staining by using an antibody directed to nitrotyrosine produced by nitration of tyrosine, and (2) a method of detecting singlet oxygen produced by reaction of ONOO⁻ and H₂O₂ on the basis of light emission at 1.3 μm. It is disclosed that although method (1) achieves high specificity and has been widely used, the method has a problem in that ONOO⁻ cannot be detected in real time by applying the method to a living cell system, because staining should be performed with antibodies. In addition to the aforementioned two methods, it is also disclosed that (3) a chemiluminescence method using luminol, and (4) a fluorometric detection method using a fluorescence probe to detect overall active oxygen species such as 2',7'-dichlorodihydrofluorescein (DCFH) have been used. **However, these methods fail to achieve specificity, and therefore reliable detection cannot be expected even if various inhibitors are used. For example, it is disclosed that in the method (4), DCFH reacts with**

both of NO and superoxide to give an increase in fluorescence, and therefore it is impossible to distinguish whether ONOO⁻ is detected, or NO or superoxide is detected.

Reference is also made in the originally filed application to WO 01/64664 (which is used in the present rejection) for the fact that arylated fluorescein derivatives are known to be useful reagents for measuring active oxygen (International Patent Publication WO01/64664).

However, it is disclosed that this publication neither suggests nor teaches that the fluorescein derivatives have reactivity with peroxynitrite.

Still further, **Applicants originally filed application includes disclosure of the specific measurement of peroxynitrite even in the presence of superoxide and NO, which are precursors of peroxynitrite, as see, for example, the second full paragraph on page 2, and page 5, the paragraph beginning at the bottom of the page. Moreover, Examples of the unexpected specific measurement of peroxynitrite in the presence of superoxide and NO are provided in Applicants' originally filed specification.** In this regard, attention is directed to Applicants' Examples wherein the results are shown in Table 1. As disclosed in Example 1, the measuring reagents of the present invention (HPF and APF) gave an increase in fluorescence by the reaction with peroxynitrite, whilst the reagents did not react with superoxide nor NO, and gave substantially no increase of fluorescence. DCFH greatly increased fluorescence by the reaction with peroxynitrite, and it also increased fluorescence by the reactions with both of superoxide and NO. These results are disclosed as revealing that peroxynitrite alone is successfully measured specifically by using the measuring reagent of the present invention without being affected by superoxide or NO.

In contrast, to the showings in Applicants' originally filed application, WO 01/64664, which is specifically discussed in Applicants' originally filed application and includes the

inventors of the present application, does not teach or suggest a method of measuring peroxy nitrite, nor does WO 01/64664 teach or suggest a method of measuring peroxy nitrite without being affected by NO or superoxide.

The rejection does not provide any suitable teaching or suggestion for measuring peroxy nitrite, and certainly does not show any expectation of success in measuring peroxy nitrite when it would be expected that NO and superoxide would be expected to interfere with such measurement.

The rejection appears to rely upon Aldini to try and establish obviousness of measuring peroxy nitrite. However, Aldini is directed to a method of evaluation of lipid antioxidant activity of a sample by accurately measuring the antioxidant activity of both the lipid compartment and the aqueous compartment. Aldini merely mentions various free radicals or other reactive oxygen species in paragraphs [0046] and [0048], which include both peroxy nitrite and superoxide anion radical and nitric oxide radical. However, Aldini does not teach or suggest the specific reaction with peroxy nitrite in the manner recited in Applicants' claims that provides the specific measure of peroxy nitrite. At most, Aldini is further evidence of Applicants' unexpected specific measurement of peroxy nitrite.

The Interview Summary mailed November 23, 2009, discusses anticipation of a species that is at once envisaged by a genus. However, in the present situation, the rejection is not an anticipation rejection. In this regard, the Examiners are reminded that the anticipation rejection has been withdrawn because Nagano does not disclose measuring peroxy nitrite. Moreover, the measurement of peroxy nitrite in the manner recited in Applicants' claims is not "readily envisaged". Nagano provides disclosure of measuring various types of reactive oxygen's including superoxide and nitrogen monoxide, as see Table 1 of Nagano. However, Nagano does

not teach or suggest measuring peroxy nitrite let alone specifically measuring peroxy nitrite in the presence of superoxide or NO. Certainly, this is unexpected and not readily envisaged from any disclosure in Nagano.

Accordingly, the rejection of record is without appropriate basis and should be withdrawn.

Response To Obviousness-Type Double Patenting Rejections

The following obviousness-type double patenting rejections are set forth in the Office Action.

(a) Claims 2-3 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 5 and 13-14 of U.S. Patent No. 7,087,766 as evidenced by US 2002/0182736 A1 to Aldini et al.

(b) Claims 2-3 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 of U.S. Patent No. 7,378,282 as evidenced by US 2002/0182736 A1 to Aldini et al..

With regard to these grounds of rejection, Applicants initially once again note that Patent No. 7,087,766 is the national stage of WO 01/64664. Accordingly, for at least the reasons set forth above, U.S. Patent No. 7,078,766 does not render obvious the subject matter recited in Applicants' independent claim 3 and claim 2 dependent therefrom.

Moreover, claims 5 and 13-14 of U.S. Patent No. 7,087,766 are merely directed to the measurement of reactive oxygen, and claims 1 and 2 of U.S. Patent No. 7,378,282 are directed to hypochlorite ion. The claims of U.S. Patent No. 7,087,766 and U.S. Patent No. 7,378,282 do not teach or suggest any desirability of measuring peroxy nitrites or the surprising capability of

specifically measuring peroxy nitrites without being affected by NO or superoxide. Accordingly, the claims of neither of these patents, whether taken alone or considered with Aldini, would arrive at Applicants' claimed subject matter.

Applicants therefore submit that the rejections of record are without appropriate basis and should be withdrawn.

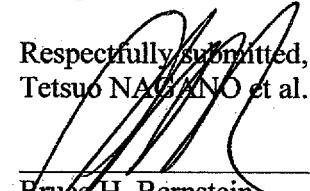
CONCLUSION

In view of the foregoing, the Examiner is respectfully requested to reconsider and withdraw the restriction requirement and the rejections of record, and allow each of the pending claims.

Applicants therefore respectfully request that an early indication of allowance of the application be indicated by the mailing of the Notices of Allowance and Allowability.

Should the Examiner have any questions regarding this application, the Examiner is invited to contact the undersigned at the below-listed telephone number.

Respectfully submitted,
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